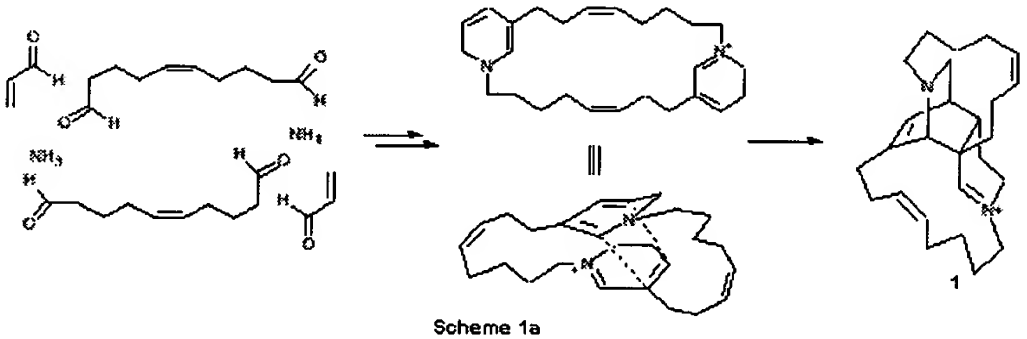
Biomimetic Synthesis

The beautiful simplicity with which Nature assembles complex molecular frameworks is at tim breathtaking. We are attempting to investigate some of these intricate pathways, and uncover t mechanisms that they follow. One way of probing a postulated biosynthetic route is by looking into t chemical feasibility of a key step or steps *in vivo*, thereby developing a biomimetic synthesis. We a presently applying this approach to investigate our proposed biosynthetic routes to several interesti natural products, derived from both marine sponges and terrestrial fungi.

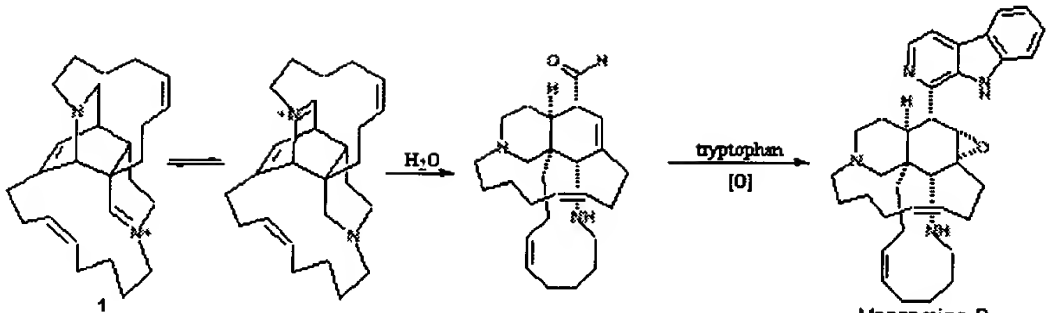
The Biosynthesis of Sponge Alkaloids

The continuous discovery of new marine natural products has provided organic chemists with a vast array c novel structures as synthetic targets. A lot of the natural products produced by sponge species are cytoto and hence represent potential sources of drugs for chemotherapy.



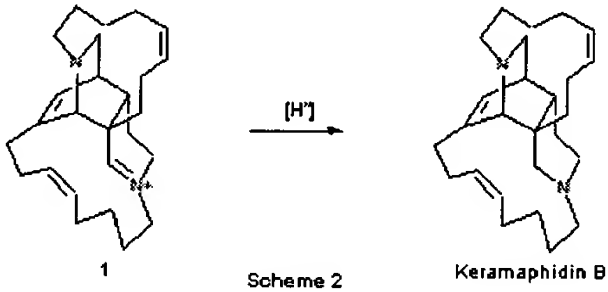
Scheme 1a

Our group is interested in the synthesis and biosynthesis of marine sponge alkaloids, particularly thc derived from 3-substituted pyridines. Previously we have proposed that the complex manzamine alkaloi could be derived from simple 3-alkylpyridine precursors (Scheme 1a&b).[1]



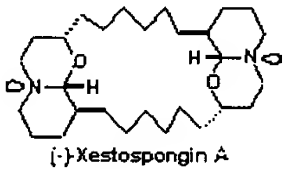
Scheme 1b

We have verified this hypothesis by the biomimetic synthesis of the sponge alkaloid keramaphidine B. Keramaphidine B represents the reduction product of the putative intermediate **1**, proposed Diels Alc product (Scheme 2).



Scheme 2

Our successful biomimetic synthesis of several compounds from another class of sponge alkaloids, the xestospongins, has provided strong support for our proposed biosynthetic pathway to these compounds.[4]

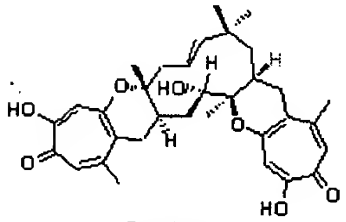


(-)-Xestospongin A

Stemming from these biomimetic studies, we are also interested in the total synthesis of several spon metabolites , including the cyclostellettamines A-F, motuporamines A and B and pyrinodemin A

Biomimetic Synthesis of Fungal Metabolites

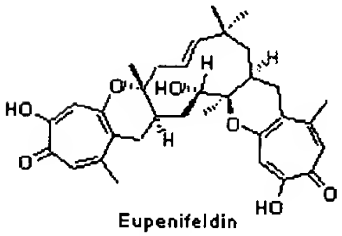
Tropolone Natural Products



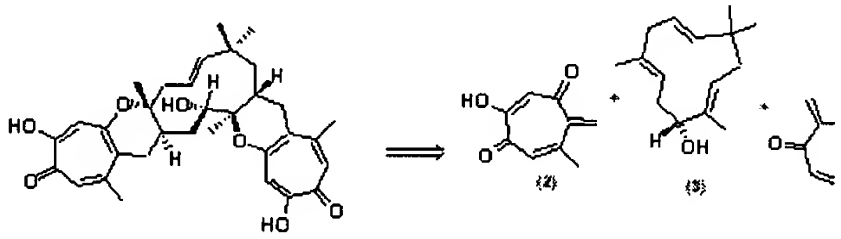
Pycnidione

Pycnidione, eupenifeldin and epolone B are members of a family of fungal metabolites that were recently isolated, and which have dei interesting biological activity.

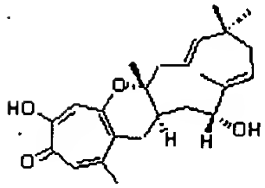
We propose that these fungal metabolites may be biosynthesised by the tropolones to a sesquiterpene such as humulene (Scheme 3). Thus we that these natural products could be made by the hetero Diels-Alder reac tropolone quinone-methide **2** with a sesquiterpene **3**.



Eupenifeldin



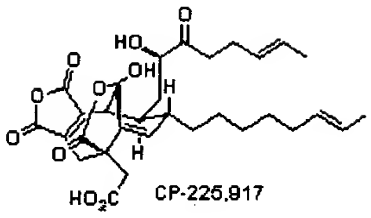
Scheme 3



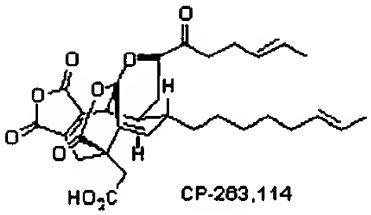
Epolone B

Studies towards the synthesis of the quinone-methide-tropolone precu currently in progress. To investigate the chemical feasibility of the hetero Diels-Alder reaction as a biomimetic strategy, model studies h undertaken with a benzotropolone analogue.[5]

CP-225,917 and CP-263,114

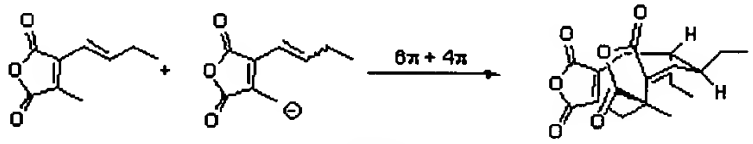


CP-225,917



CP-263,114

The natural products CP-225,917 and CP-263,114 were recently isolated from an unidentified fungal spec characterised as inhibitors of both squalene synthase and the Ras-farnesyl transferase. We are presently inv a biomimetic approach to these compounds centred around construction of the nine-membered ring by a 6π cyclodimerisation (Scheme 4).[6, 7]



Scheme 4

References

1. J. E. Baldwin & R.C. Whitehead, "On the biosynthesis of manzamines," *Tetrahedron Lett.* **33**, 2 (1992).

2. J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. White Boughflower, I. M. Mutton & R. J. Upton, "Investigations into the manzamine alkaloid biosynthetic h *Angew. Chem. Int. Ed.* **37**, 2661-2663 (1998). [journal link]

3. J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, & R. C. "Studies on the biomimetic synthesis of the manzamine alkaloids," *Chem. Eur. J.* **5**, 3154-3161 (199 link]

4. J. E. Baldwin, A. Melman, V. Lee, C. R. Firkin & R. C. Whitehead, "Biomimetic sy (-)-Xestospongin A, (+)-Xestospongin C, (+)-Araguspongine B and the correction of thei configurations," *J. Am. Chem. Soc.* **120**, 8559-8560 (1998). [journal link]

5. J. E. Baldwin, A. V. W. Mayweg, K. Neumann & G. J. Pritchard "Studies toward the biomimetic s tropolone natural products via a hetero Diels-Alder reaction," *Org. Lett.* **1**, 1933-1935 (1999). [jo

6. J. E. Baldwin, A. Beyeler, R. J. Cox, C. Keats, G. J. Pritchard, R. M. Adlington & D. "Reinvestigation of the dimerisation process forming isoglaucanic acid," *Tetrahedron* **55**, 7363-73 [journal link]

7. J. E. Baldwin, R. M. Adlington, F. Roussi, P. G. Bulger, R. Marquez & A. V. W. Mayweg, "Studi the biomimetic synthesis of the nonadrides CP-225,917 and CP-263,114," *Tetrahedron* **57**, 7409-74 [journal link]

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I joined Exeter College in October 2000 as a fellow and tutor in Organic Chemistry. I also currently serve as a panel referee for Tetrahedron Letters. I am a native of Hong Kong and obtained my B.Sc. from the University of Hong Kong was awarded the Croucher Foundation studentship and completed my M.Phil. studies with Prof. Kin-Fai Cheng at the same institute. My M.Phil. research concerned the synthesis of anti-implantation indole alkaloid. A Croucher Foundat scholarship brought me to Oxford and the Dyson Perrins Laboratory. I completed my D.Phil. studies, under the direct Prof. Sir Jack E. Baldwin, in the synthesis of HIV protease inhibitors. I remained in Prof. Baldwin's group as a postdoc research assistant and was subsequently appointed departmental research assistant at the Dyson Perrins Laboratory maintaining full collaboration with Prof. Baldwin.

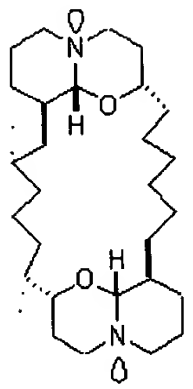
From 1992 to 2000 I tutored Organic Chemistry to First Year Biochemists at Hertford College. From 1999-2000 I deli revision classes to third year Hertford chemists. I also conduct weekly problems classes for postgraduate students an postdoctoral workers in the Baldwin group. My teaching covers all aspects of Organic Chemistry.

Research Interest

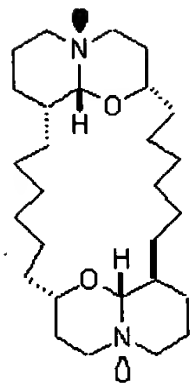
My research centres around synthetic Organic Chemistry. Nature has produced an impressively diverse range of natu products with potent biological activities. The sources of these compounds ranged from microorganisms to plants an animals. Very often these compounds are produced in minute quantities by the organisms and it would be impractica harvest these compounds from the natural sources. Chemical synthesis offers an alternative solution to the supply problem and the opportunities for preparing structural analogues. The chemical synthesis of a natural product also s to verify or sometimes disprove a proposed structure. Organic synthesis has been described both as an art and a scie The logical disconnection of a complex molecule into simpler building blocks and the various possible ways these bu blocks are assembled constitute a synthetic plan. An elegant synthetic plan requires one's imagination and creativity, which is certainly a form of art. The science part of organic synthesis is through the understanding of reaction mechanisms, which provides Organic Chemists the abilities to predict the outcome of reactions. It opens up the possibilities to design and invent new chemical reactions.

My current research interest is the synthesis of marine sponge alkaloids. Here are a few sponge alkaloids that are chemically synthesised and two projects that are currently under investigation in my laboratory:

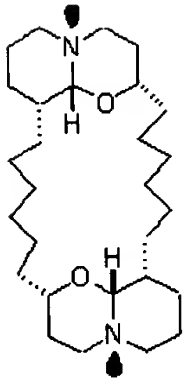
Completed synthesis: (-)-Xestospongin A, (+)-Xestospongin C and (+)-Araguspongine B; Cyclostellettamines A-F; Keramaphidin B.



(-)-Xestospongin A



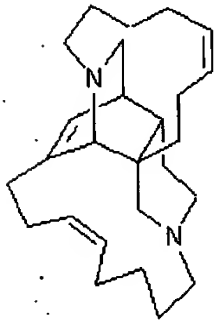
(+)-Xestospongin C



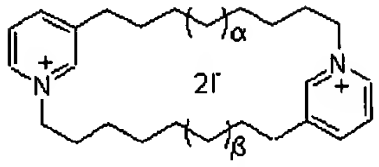
(+)-Araguspongine B

514/229.5

(pentacyclo polycyclic ring (5 rings) structure



Keramaphidin B



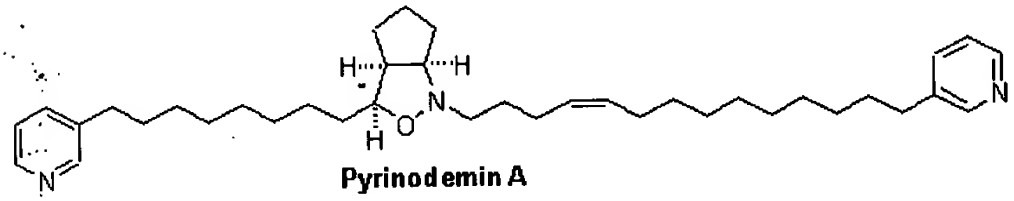
Cyclostellettamines A-F

A: $\alpha=\beta=5$
B: $\alpha=5, \beta=6$
C: $\alpha=\beta=6$
D: $\alpha=5, \beta=7$
E: $\alpha=6, \beta=7$
F: $\alpha=\beta=7$

Current research projects:

A) Total synthesis of Pyrinodemin A

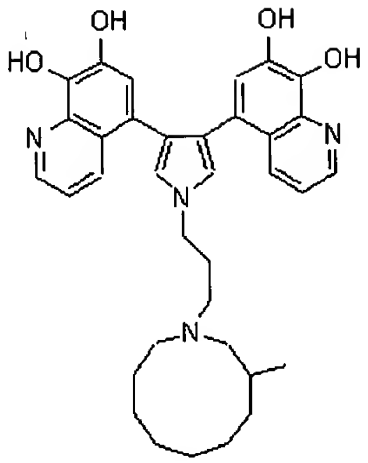
Pyrinodemin A is a novel *bis*-pyridine alkaloid isolated from the marine sponge *Amphimedon* sp. in 0.0001 (wet weight) yield. It possesses cytotoxicity against murine leukaemia L1210 cells (IC_{50} 0.058 ?g/mL) and epidermoid carcinoma cells (IC_{50} 0.5 ?g/mL) *in vitro*.



Pyrinodemin A

B) Total synthesis of Halitulin

Halitulin is a novel *bis*-quinolinylpyrrole alkaloid isolated from the sponge *Haliclona tulearensis* in 0.56% weight) yield. It is cytotoxic against P-388 murine leukaemia cells (IC_{50} 0.025 ?g/mL), A-549 human lung carcinoma cells (IC_{50} 0.012 ?g/mL), HT-29 human colon carcinoma cells (IC_{50} 0.012 ?g/mL) and MEL-28 human melanoma cells (IC_{50} 0.025 ?g/mL) *in vitro*.



Halitulin

Recent Publications

- Jack E. Baldwin, Artem Melman, Victor Lee, Catherine R. Firkin and Roger C. Whitehead, The Biomimetic Synthesis of (+)-Araguspongine B, (-)-Xestospongin A, (+)-Xestospongin C and the Correction of their Absolute Configurations, *J. Am. Chem. Soc.*, **1998**, *120*, 8559-8560.
- Jack E. Baldwin, Timothy D. W. Claridge, Andrew J. Culsaw, Florian A. Heupel, Victor Lee, David Spring and Roger C. Whitehead and in part Robert J. Boughtflower, Ian M. Mutton and Richard J. U Investigations into the Manzamine Alkaloid Biosynthetic Hypothesis, *Angew. Chem. Int. Ed.*, **1998**, *3* 2661-2663.
- Jack E. Baldwin, David R. Spring, Catherine E. Atkinson and Victor Lee, Efficient synthesis of the sponge alkaloids Cyclostellettamines A-F, *Tetrahedron*, **1998**, *54*, 13655-13680.
- Jack E. Baldwin, Timothy D. W. Claridge, Andrew J. Culshaw, Florian A. Heupel, Victor Lee, Davic Spring and Roger C. Whitehead, Studies of the Biomimetic Synthesis of the Manzamine Alkaloids, *C Eur. J.*, **1999**, *5*, 3154-3161.
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